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GREEN SYNTHESIS OF CINNAMIC ACID AND DERIVATIVES USING PALLADIUM N-HETEROCYCLIC CARBENE CATALYST

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ABSTRACT

Cinnamic acids and esters are widely used intermediates for the fine chemical and pharmaceutical Industries. In the current studies, cinnamic acids and cinnamates were synthesized via Mizoroki-Heck cross-coupling reaction mediated through palladium N-heterocyclic carbene as catalyst. The catalyst was synthesized through double N-benzylation of benzimidazole to yield 1,3-di benzylbenzimidazolium bromide (the pre-carbene) (2). The pre-carbene was then reacted with palladium bromide ($PdBr_2$) in 3-methylpyridine, to yield the pre-catalyst (Dibromido[(1,3-dibenzylbenzimidazole-2-ylidene) (3-methylpyridine)] palladium (II) (3)). The intermediates and the pre-catalyst were characterized using ^1H and FT-IR analyses which supported the proposed structures. The pre-catalyst was used to develop a method for the synthesis of cinnamic acids and cinnamates via Mizoroki-Heck cross-coupling reactions. In the substrate scope studies, the pre-catalyst (3) demonstrated excellent air and moisture stability and compatibility with both activated and un-activated and deactivated aryl bromides.

***Key words**: Green synthesis, Cinnamic acids, Benzimidazole, Complexes*

INTRODUCTION

Cinnamic acids, esters and amides have a long history of human use as a component of plant-derived flavours and perfumes (De *et al*., 2011, Ibrahim *et al*., 2022). A large number of cinnamates have been found to show significant biological activity against cancer and tuberculosis (Cardona, 2012). The most common approach towards the synthesis of these valuable materials include Knoevenagel, Reformatsky and Perkin condensations. These methods suffers from many limitations, such as the multistep approach and the use of toxic and expensive acyl intermediates. An alternative to these methods are the palladium-catalyzed coupling reactions which are mild and straightforward for the synthesis of cinnamates (Ibrahim *et al*., 2016).

The palladium catalyzed Heck reaction is a widely accepted method for the synthesis of substituted alkenes from organic moieties bearing an appropriate leaving group. In this reaction, the aryl halide (iodides, bromides and chlorides) react with terminal alkenes such as styrene, acrylic acid and acrylate in the presence of a base and a suitable palladium catalyst to yield internal alkenes such as stilbenes, cinnamic acids, cinnamates and cinnamides respectively (Shakil-Hussein *et al*., 2014; Hamasaka and Uzomi, 2018; Jin *et al.,* 2018; Li, *et al*., 2019) These are commonly used intermediates for the fine chemical and pharmaceutical industries. Unfortunately, the large volume of organic solvents and palladium phosphine catalysts discharged as effluents form the cross coupling reactions are toxic to the environment (Levin *et al*., 2015).

In order to alleviate the pollution caused by the discharge of harmful substances in to the environment, researchers have resort to the use of greener synthetic protocols as alternative to the use of conventional organic solvents. This include among others; the solvent-less (neat) reactions (Tanaka, 2003), use of ionic liquids (Jessop *et al*., 2007), reactions in aqueous media (Li*.,* 2005) and use of recyclable systems (Ibrahim *et al*., 2016).

In addition to our previous efforts in developing easy and environmental friendly methods for cross coupling reactions (Ibrahim *et al*., 2016, 2022, Nguyen *et al*., 2017) We wish to report the synthesis of new Benzimidazolium based - Palladium *N*-heterocyclic carbene complex, its application in Mizoroki-Heck reaction as well as a possible recycling protocol.

EXPERIMENTAL

Materials and Instrumentation

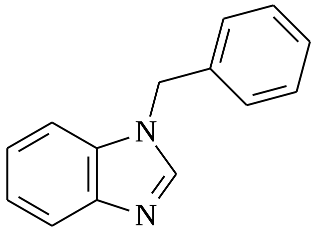
Materials from the synthesis of carbene precursors and the palladium-carbene complex were purchased from Sigma Aldrich and used as received. All solvents used were of analytical grade, purchased from Analare or Loba Chemie PVT limited, India. The products were analysed using Supeico pre-coated silica gel 60 F254 Aluminium sheets and were purified using column chromatography. The 1H NMR spectral data were recorded on 500 MHz NMR machine (Joel 1500 model). Chemical shifts were recorded in ppm using tetramethylsilane as reference and $CDCl_3$ as solvent. Fourier transform infrared (FT-IR) spectra were recorded using an Agilent technology FT-IR spectrophotometer in wavenumber (cm^{-1}).

Synthesis of NHC Pre-cursor and its Corresponding Palladium Complex

N-Benzylbenzimidazole, the carbene precursor and its complex were synthesized using a modification of earlier published procedures (Ibrahim *et al.*, 2022; Suleiman *et al.*, 2023) as follows:

Synthesis of 1-Benzylbenzimidazole

Benzimidazole (5.0 mmol), Benzyl bromide (5.5 mmol), potassium hydroxide (6.0 mmol) and potassium carbonate (6.0 mmol) were introduced into a two necked round bottom flask fitted with a magnetic stir bar and a reflux condenser. The mixture was dissolved in 40 cm^3 anhydrous acetonitrile and refluxed for 24 hours. After completion of the reaction, the mixture was cooled to room temperature and the solvent was removed by rotary evaporator. The crude product was extracted three times with 50 cm^3 ethyl acetate and 20 cm^3 water. The combined ethyl acetate extract was dried using anhydrous magnesium sulfate. The solvent was removed using rotary evaporator and the crude products was purified using silica-gel column chromatography.



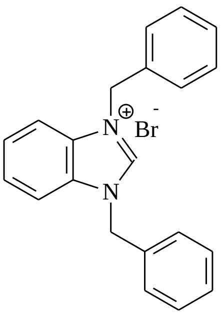
1-Benzylbenzimidazole (1)

Yellow solid, 87 % yield; M. P. 115 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.25 (s, H, NCHN); 7.88 (d, H, CH aromatic, *J* = 8.0 Hz); 7.38-7.29 (m, 6H, CH aromatic, *J* = 5.6 Hz); 7.24 (d, 2H, CH aromatic, *J* = 7.6 Hz); 5.43 (s, 2H CH_2) FT-IR: 3028 cm^{-1} (C-H), 1490 cm^{-1} (C = N), 1447 cm^{-1} (C = C), respectively.

Synthesis of 1,3-Dibenzylbenzimidazolium Bromide

1-Benzylbenzimidazole (1) (1.2 mmol) and benzyl bromide (1.5 mmol) were taken up into a cleaned and oven dried 25 cm^3 round bottom flask, tetrahydrofuran (10 cm^3) was added. The mixture was refluxed overnight at 70°C. After the reaction was completed, the product was cooled and decanted to afford the crude 1,3-dialkylbenzimidazolium salt which was then washed several times with diethyl ether. The product was analyzed using TLC (50% ethyl acetate and 50% n-hexane) and washed further with ether, until no free n-alkyl benzimidazole was observed.

1,3-Dibenzylbenzimidazolium bromide (2)

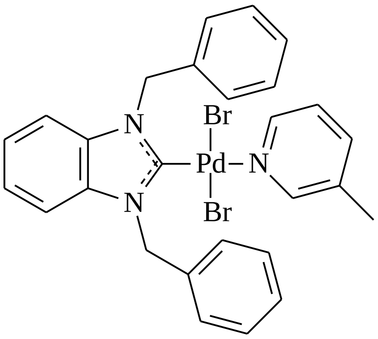


White solid, 63 % yield, M.P. 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 11.62 (s, 1H, NCHN); 7.61-7.28 (m, 14H, CH aromatic, J = 2.8 Hz); 5.89 (s, 2H, NCH_2); FT-IR: 2948 cm^{-1} (C-H), 1559 cm^{-1} (C=N), 1458 cm^{-1} (C=C).

Synthesis of the Palladium Complex

Under nitrogen atmosphere, 1,3-dibenzylbenzimidazolium bromide (0.50 mmol), Palladium (II) bromide (0.50 mmol) and potassium carbonate (2 mmol) were introduced into a cleaned and dried round bottom flask (25 cm^3). The mixture was dissolved in 3-methyl pyridine (5 cm^3) and heated for 48 hours at 100°C. After the reaction was completed, the pyridine was evaporated and the dried product was dissolved in dichloromethane and passed through a micro column packed with silica gel. The eluent was dried and the crude product was further purified by recrystallization using dichloromethane and ether to afford yellowish solid (Ibrahim *et al.*, 2016).

Dibromido[(1,3-dibenzylbenzimidazole-2-ylidene) (3-methylpyridine)] palladium (II) (3)



Brown solid, isolated yield = 82 %, M. P= 168°C; FT-IR (cm^{-1}): 2930, 1607, 1410.

Procedure for the Synthesis of Cinnamic acids

Palladium complex (**3,** 0.5 mol %), aryl halide (1.0 mmol), acrylic acid/methyl acrylate (1.5 mmol), KOH (2.0 mmol) and water (4.0 mL) were introduced into a 15 mL round-bottom flask fitted with a magnetic stir bar and reflux condenser. The mixture was stirred at 90°C for 2 hours. Progress of the reaction was monitored using TLC until no free aryl bromide was observed. The reaction was stopped and cooled down to room temperature. The crude product was acidified using 2 mL of 1M HCl prior to the extraction. The product was then extracted three times with 10 mL of ethyl acetate. The ethyl acetate extracts were combined and dried with anhydrous magnesium sulfate. The solvent was removed in a rotary evaporator to afford the corresponding cinnamic acid.

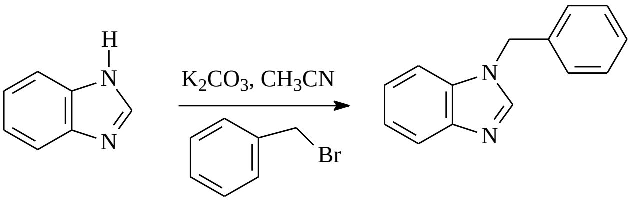
Recycling: At the end of the cycle, to the remaining aqueous layer, a fresh portion of the bromobenzene, acrylic acid and KOH were added this time around without adding any catalyst. The flask was mounted to the condenser and the reaction was repeated for another cycle using the same conditions described above.

Procedure for the Synthesis of Cinnamates

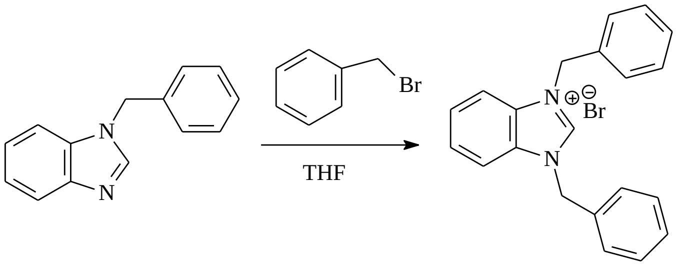
Palladium complex (**3,** 0.5 mol %), aryl bromide (1.0 mmol), methyl acrylate (1.5 mmol), KOH (2.0 mmol) and anhydrous DMF (4.0 mL) were introduced into a 15 mL round-bottom flask fitted with a magnetic stir bar and reflux condenser. The mixture was stirred at 110°C for 4 hours. Progress of the reaction was monitored using TLC until no free aryl bromide was observed. The reaction was stopped and cooled down to room temperature. The product was extracted three times with 10 mL of ethyl acetate. The ethyl acetate extracts were combined and dried with anhydrous magnesium sulfate. The solvent was removed in a rotary evaporator to afford the corresponding cinnamate.

RESULTS AND DISCUSSION

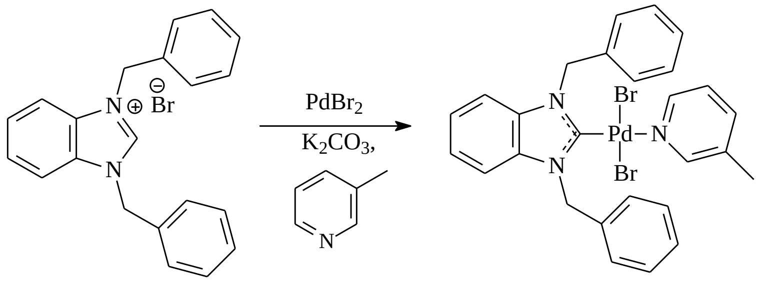
Synthesis of the Carbene Precursor, Imidazolium Salt and the Palladium N-Heterocyclic Carbene Complex



Scheme 1: Synthesis of 1-Benzylbenzimidazole (**1**)



Scheme 2: Synthesis of 1,3-Dibenzylbenzimidazolium salt (**2**)



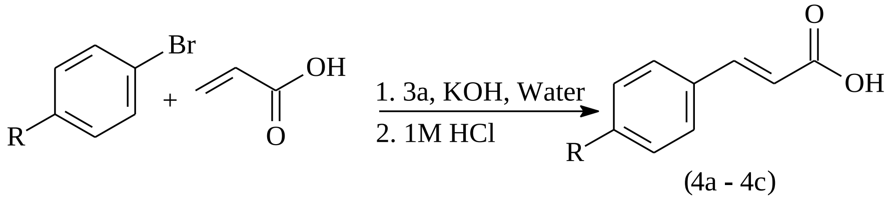
Scheme 3: Synthesis of Dibromido[(1,3-dibenzylbenzimidazole-2-ylidene) (3-methylpyridine)] palladium (II) (**3**)

The synthesis of *1-benzyl benzimidazole (**1**)* is indicated in scheme 1 above. It was obtained as yellow solid with isolated yield of 87 %. Melting point of the product is the same as the value reported in the literature. The proton NMR and the FT-IR of the product indicate the presence of signals which are in agreement with the structure (Suleiman, *et al.*, 2023).

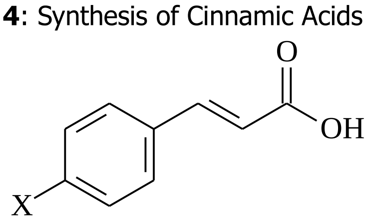
The carbene precursor, 1,3-dibenzylimidazolium salt (**2**) was synthesized as summarized in scheme 2. It was obtained in good yield (63 %). Characterization data of the compound is in agreement with its structure. The ^{1}H NMR spectrum indicate the presence of a downfield signal at 11.6 ppm which is assigned to be the acidic proton (NC*H*N) of 1,3-dibenzylbenzimidazolium salt (**2**). Moreover, the proton on the methylene carbon (CH_2) of the benzyl group was found to resonate at δ 5.9 ppm as a sharp singlet peak, further confirming the formation of the expected benzimidazolium salt. The multiplet signal for the CH aromatic protons were observed within the range of 7.61-7.80 ppm and this show agreement with the values reported in the literature (Yaqub *et al.*, 2022). The FT-IR data clearly indicate the presence of C=N with bands ascribed to (C=N) being observed at 1548.7 to 1593.36 cm^{-1} for benzimidazolium salts.

The pre-catalyst (*Dibromido[(1,3-dibenzylbenzimidazole-2-ylidene) (3-methylpyridine)] palladium (II) (**3**)*) was synthesized from the reaction of 1,3-dibenzylbenzimidazolium (**2**) salt with $PdBr_2$ in 3-methylpyridine, using K_2CO_3 as base as described previously on scheme 3. The complex was characterized using FT-IR and melting point. The melting point was found to be 168^{o}C. The change in melting point of the complex when compared with that of the free 1,3-dibenzyl benzimidazolium salt, coupled with the observed variation in the FT-IR absorption bands confirms the coordination of both the ligand precursor and the pyridine molecules with the palladium metal.

Evaluation of the Activity of Dibromido[(1,3-dibenzylbenzimidazole-2-ylidene) (3-methylpyridine)] palladium (II) (3) as Catalysts for the Synthesis of Representative Cinnamic Acids and Cinnamates.



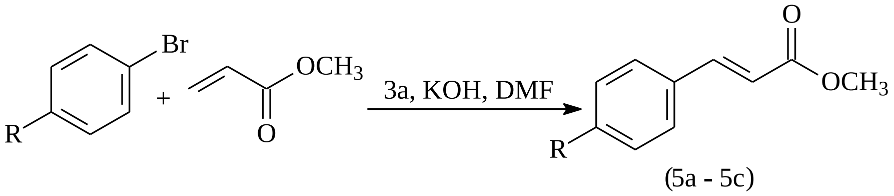
Scheme 4: Synthesis of Cinnamic Acids



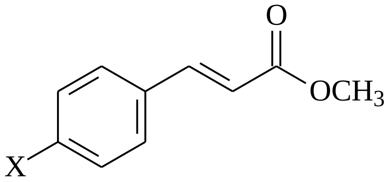
4a: X=H; Cinnamic acid, white solid, 88 % yield, M.P= 131^{o}C

4b: X=OCH_3; 4-Methoxycinnamic acid, white solid, 79 % yield, M.P= 198^{o}C

4c: X=CH_3CO; 3-(4-acetylphenyl)prop-2-enoic acid, yellow solid, 91 % yield, M.P= 222^{o}C



Scheme 5: Synthesis of Cinnamates



5a: X=H; Methyl cinnamate, colourless oil, 86 % yield

5b: $X=OCH_3$; Methyl -3-(4-methoxyphenyl)prop-2-enoate, brownish thick oil, 78 % yield.

5c: $X=CH_3CO$; Methyl-3-(4-acetylphenyl)prop-2-enoate, brownish thick oil, 88 % yield.

The catalytic activity of the Dibromido[(1,3-dibenzylbenzimidazole-2-ylidene) (3-methylpyridine)] palladium (II) (**3**) was evaluated in the synthesis of valuable compounds. Cinnamic acid derivatives are versatile intermediates for the production of drugs, cosmetic and perfumes (Bhatia *et al*., 2007 and Gunia-Krzyzak *et al*., 2018). This important compound can be efficiently synthesized using the palladium-catalyzed Mizoroki-Heck coupling reaction. Using a previously optimized reaction protocol (Ibrahim *et al*., 2022), the complex was employed as catalyst for the synthesis of some representative cinnamic acids and cinnamates. Using water as sole solvent, in the presence of potassium hydroxide, substituted and unsubtituted aryl bromides react smoothly with acrylic acid or acrylate to yield the corresponding cinnamic acid in good to excellent yield. For example, the use of bromobenzene as aryl halide yielded *E*-Cinnamic acid as major product with isolated yield of 88 %. However, substituted bromobenzene i.e 4-bromo anisole and 4-bromoacetophenone yielded the corresponding cinnamic acids ; 4-methoxy cinnamic acid (89%) methyl-3-(4-acetophenoxy)prop-2-enoic acid (91 %), respectively. The slight increase in yield observed with deactivated aryl bromide is well documented in the literature, that aryl halides having electron withdrawing group react faster towards cross coupling than unsubstituted and aryl halides with electron donating substituents (Shakil-Hussein, 2014; *et al*., Nguyen *et al*., 2017).

Upon the use of methyl acrylate instead of acrylic acid and anhydrous DMF instead of water as solvent, the aryl bromide coupled smoothly to yield the corresponding cinnamates as product. Similar trend in yield was observed as the former.

In the recycling studies, only 48% coupling product was isolated after the second cycle which reduced down to 22 % in the third cycle. This indicates a significant loss in catalytic activity which could be as a result of palladium leaching to the product or catalyst deactivation due to other factors.

CONCLUSION

The synthesis of palladium catalysts with very good activity towards the synthesis of cinnamic acid and cinnamates was achieved. However, the catalyst show poor recyclability which could be addressed by immobilization on a solid support such as Merifield and silica resins.

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REFERENCES

Bhatia, S., Wellington, G. A., Cocchiara, J., Lalko, J., Letizia, A. M. Api (2007) "Fragrance material review on cinnamyl cinnamate" *Food and Chemical Toxicology*, 566, 308 https://doi.org/10.1016/j.fct.2007.09.030.

Cardona P-J (2012). Understanding Tuberculosis—New Approaches To Fighting

Against Drug Resistance. *InTech Croatia pub.*, 15, 337

De P., Baltas M., Bedos-Belval F. (2011) "Cinnamic Acid Derivatives as Anticancer Agents- A Review" *Curr. Med. Chem.* 18, 1672

Gladysz, J. A.; Curran, D. P. (2002) "Fluorous Chemistry: From Biphasic Catalysis to a Parallel Chemical Universe and Beyond" *Tetrahedron,* 58, 3823.

Gunia-Krzyzak, A., Slocynska, K., Popiol, J., Koczurkiewicz, P., Marona, H., Pekala, E. (2018) "Cinnamic acid derivatives in cosmetics: current use and future prospects" *International Journal of Cosmetic Science*, 40, 356 https://doi.org/10.1111/ics.12471.

Hamasaka, S., I., Uozumi, Y. (2018). "A Palladium NNC-pincer complex as an efficient catalyst precursor for the Mizoroki−Heck Reaction" *Adv. Synth. Catal.***,** 360, 1833 http://doi.org/10.1002/adsc.201800099.

Ibrahim, M.B., Rufa'i, S. A., Yaqub, H. U., Suleiman, U. B. (2022) "Efficient palladium *n*-heterocyclic carbene catalytic system for the synthesis of cinnamic acid and derivatives in water" *Bulgarian Chemical Communications,* 54, 2. 172-181. DOI: 10.34049/bcc.54.2.5478

Ibrahim, M. B., Suleiman R., Fettouhi M., El Ali, B. (2016) "A silica-supported palladium-bis(oxazoline) complex efficiently catalyzes the synthesis of cinnamic acid derivatives via Mizoroki–Heck coupling reactions" *Transit. Met. Chem.* DOI 10.1007/s11243-016-0098-4

Ibrahim, M. B., Malik, I., Mansour, W., Sharif, M., Fettouhi, M., El Ali, B. (2018) "Novel (N-heterocyclic carbene)Pd(pyridine)Br complexes for carbonylative Sonogashira coupling reactions: catalytic efficiency for arylalkynes, alkylalkynes and dialkynes" *Appl. Organometal. Chem*. 32, 4 https://doi.org/10.1002/aoc.4280

Ibrahim, M. B., Malik, I., Mansour, W., Sharif, M., Fettouhi, M., El Ali, B. *(*2018) "Efficient N-heterocyclic carbene palladium(II) catalysts for carbonylative Suzuki-Miyaura coupling reactions leading to aryl ketones and diketones" *J. Organometal. Chem. 859* 859 44. https://doi.org/10.1016/j.jorganchem.2018.01.028.

Jessop, P. G.; Leitner, W. (2007) Chemical Synthesis Using Supercritical Fluids, 1-36; Wiley VCH.

Jin, L., Qian, L., Sun, N., Hu, B., Shen, Z., Hu, X. (2018). "Pd-Catalyzed reductive heck reaction of olefins with aryl bromides for Csp^2–Csp^3 bond formation" *Chem. Commun.* 54*,* 5752. http://doi.org/10.1039/C8CC02571A.

Levin, E., Ivry, E., Diesendruck, C. E., Lemcoff, N. G. (2015) *Chem. Rev.* 115, 4607 https://doi.org/ 10.1021/cr400640e.

Li, C. (2005) "Organic reactions in aqueous media with a focus on carbon – carbon bond formations: decade update" *Chem. Rev.* 105, 3095.

Li, W., Li, C. Y., Xiong, H. Y., Liu, Y., Huang, W. Y., Ji, G. J., Jiang, Z., Tang, H. T., Pan, Y. M., Ding, Y. J. (2019) "Constructing mononuclear palladium catalysts by precoordination/solvothermal polymerization: recyclable catalyst for regioselective oxidative Heck reactions" *Angew. Chem. Int. Ed.*, 58, 2448 http://doi.org/10.1002/anie.201814493.

Nguyen,V. H., Ibrahim, M. B. I., Mansour, W. W., El Ali, B. M., Huynh, H. V. (2017) "Postmodification approach to charge-tagged 1,2,4-triazole-derived NHC palladium(II) complexes and their applications" *Organometallics* 36**,** 2345 https://doi.org/10.1021/acs.organomet.7b00329.

Shakil-Hussein, S. M., Ibrahim, M. B., Fazal, A., Suleiman, R., Fettouhi, M., El Ali, B. (2014) "Palladium–bis(oxazoline) complexes with inherent chirality: Synthesis, crystal structures and applications in Suzuki, Heck and Sonogashira coupling reactions" *Polyhedron*, 70, 39. http://dx.doi.org/10.1016/j.poly.2013.12.023.

Suleiman, U. B., Umar Y., Muhammad A. and Ibrahim, M. B (2023) "Corrosion inhibitive potentials of some N-alkyl benzimidazoles and their corresponding ionic liquids on a mild steel surface: experimental and theoretical approach" *Portugaliae Electrochimica Acta 41 (2023) 363-380* https://doi.org/10.4152/pea.2023410504

Yaqub, H.U., Rufa'i, S.A., Suleiman, U.B. and Ibrahim, M.B. (2022) "Synthesis of internal alkynes using new palladium n-heterocyclic carbene catalytic system" Bayero Journal of Pure and Applied Sciences, 13(1): 1 – 6 http://dx.doi.org/10.4314/bajopas.v13i1.1S